Turkish Journal of Endocrinology and Metabolism, (1998) 4 : 213-219 **ORIGINAL ARTICLE**

Evaluation of Clinical Remission in IDDM Patiets Treated With Intravenous Insulin at Onset: Three years follow-up results

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It has been suggested that strict metabolic control starting from the first weeks of insulin dependent diabetes (IDDM) is a major factor achieving clinical remission. This is usually accompanied with an increase in C-peptide secretion. Long term benefit of remisson might be related with the prevention and/or at least reduction in the rate of development of late diabetic complications.

To achieve good metabolic control, intensified insulin therapy and blood glucose monitoring accompanied to a well-planned dietary regimen and physical exercise are crucial elements. Home blood glucose monitoring has been shown to be also an important factor to obtain such a good metabolic control.

Aims of this prospective pilot study were

a) to evaluate the frequency and duration of clinical remission in newly diagnosed IDDM patients who were followed up for a period of 36 months using a unique protocol without any adjunctive immun-intervention;

b) to identify the predictive factors for remission in IDDM patients .

10 newly diagnosed IDDM patients (4 females, 6 males; mean chronological age: 14.8±6.3 yrs) who were classified WHO criteria were included in this study to test the eficacy of intensive insülin therapy (IIT) in achieving clinical remission of the disease. Patients were treated with intravenous insulin infusion at diagnosis for 2-4 days and then IIT was continued with four daily injections. A complete remission (CR) was observed in 50% of cases (5 patients); additionaly in three patients insulin requirements reduced to an incomplete remission (ICR) level (30%) No remission (NR) was obtained in the remaining two (20%). Based on remission status, initial characteristics [sex, F/M, mean age onset(years), basal / stimulated C-peptide levels (ng/ml)] were as follows. In CR Group: 1/ 4, 19.1, 1.08± 0.35/ 1.82± 0.4; In ICR Group: 3/ 0, 15.4, 0.61± 0.43 / 1.01±0.56;: In NR Group; 2/ 0, 13.8, 0.28±0.20 / 0.46 ± 0.19, respectively. All groups were evaluated at 3., 6., 12., 24. and 36. months in terms of remission status and beta cell insulin capacity. Mean length of the remission in CR group was 12.4 months . Remission for more than 2 years in one case.

In conclusion, this study indicated that remission phenomenon is more frequent than expected without immune-intervention. Older age at onset, male gender and higher initial C- peptide levels seemed to be a predictive of clinical remission in IDDM patie nts.

KEY WORDS **Insulin-dependent (Type 1) diabetes mellitus (IDDM), clinical remisson, intravenous insulin therapy**

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Introduction

Insulin dependent diabetes mellitus (IDDM; Type 1 diabetes) results from immun-mediated destruction of pancreatic beta cells in genetically susceptible individuals (1). Traditionaly, immun-intervention trials have been initiated in the early phases of clinical disease using a variety of agents with the aim of inducing and/or maintaining clinical remission. Although rather disappointing in the long-term outcome, results obtained by agents such as cyclosporin- A, azathioprine+ corticosteroids etc. have clearly shown that these drugs may increase the clinical remission rate compared with patients receiving insulin only (2-6). However, occurance of serious side effects ethically limits the use of such drugs. Other approaches which have been considered for the induction of remission include agents capable of protecting beta cells from cytotoxicity mediated by free oxygen radical scavengers (7) and intensified insulin therapy to supresss residual endogenous insulin secretion in favour of remaining beta cells, either by inducing immun tolerance or increase in beta cell regeneration (8)

The time of clinical diagnosis in the natural course of beta cell destruction is also crucial for the potential success of any type of intervention. An early diagnosis is associated with higher residual C peptide secretion and better chances of clinical remission (9-11)

It is now accepted that presentation of IDDM has been changed. Compared to 15 years ago, presentation with severe ketoacidosis or coma is less common (12) suggesting that diagnosis is now made when residual beta cell function is still present. The issue infact may contribute the increased rate of clinical remission which can be even longer than expected. In the last decades moreover, in patients who do not remit, the integrated measures of metabolic control are probably improved compared to patients diagnosed 15 years ago. Finally, attempts to preserve remaining beta cell mass at diagnosis should be taken into account with favour also for long term benefit to the patient in relation to diabetic complications (13).

AIMS

This prospective pilot study was designed to evaluate the frequency and duration of clinical remission in newly diagnosed IDDM patients who were followed up for a long term period using a unique protocol without any other adjunctive immune-intervention. The other aim was to identify the predictive factors for clinical remission of IDDM patients.

Materials and Methods

Patient Selection: 10 consecutive patients with newly onset IDDM diagnosed according to WHO criteria were recruited in the study and followed-up over a period of 36 months. Exclusion criteria were to be pregnant and to have poor general health.

Time table: Enrollment of patients in 12 months and a follow up for 36 months made the total length of this study nearly 4 years. Date of starting the study was January 1st, 1994.

Year 1: Enrollment of patients
Year 2: Recruitment completed- follow up
Year 3: Follow-up
Year 4: Completation of data
Study was completed on January 1st, 1998

Treatment Program: Patients were treated with intravenous insulin infusion in hospital at diagnosis and then IIT continued with four daily injections.

Guidelines for insulin therapy: Patients received intravenous insulin X 2-4 days at diagnosis (see protocol) and IIT afterwards; frequent blood glucose (BG) measurements required for this type of treatment was performed using a meter. Total number of BG measurements were not less than 25 times per week for the first 3 months , then not less than 15 times weekly for the remaining period of the study. We applied the same protocol consisting of the following rules. If preprandial BG values are less than 108 mg/ dl for 3 consecutive days, the insulin dose was decreased by 10 percent.; if BG levels result consistently less than 80 mg/dl, insulin dose was decreased by 20 percent. Insulin

therapy was not discontinued unless 2 hour postprandial BG levels were consistently less than 144 mg/dl. Patients with BG values above 180 mg/dl received a 10 percent increase in insulin dose or had their insulin regimen modified. Frequent telephone consultations arranged with residents and patients in order to regulate adjustments to the insulin dose.

Protocol: According to the protocol, prepared for this study, the treatment needed three elements.

1. Frequent bedside capillary BG monitoring using reactive strips and glucometer in order to adjust insulin infusion rates.

   BG monitoring was performed every two hours and recorded on a chart. BG was aimed to maintain throughout the day between 70- 150 mg/ dl.

2. Continuous infusion of insulin using an insulin pump with a "basal-bolus" scheme.

a) Administration: Insulin was administered continuously by bedside electrical syringe. İnsulin solution was reprepared every twelve hours.

b) Infusion rates
   - Initial insulin infusion rates:
     - Basal rate : 0.1 U/kg of body weight/h
     - Post meal "bolus": 0.2 U/kg of body weight/h

   These high infusion rates were necessary to overcome initial insulin resistance and to maintain as long as BG was higher than 180 mg/ dl

   - Further insulin infusion rates

   When BG rates was lower than 180 mg/ dl, insulin infusion was reduced to:
     - Basal rate : 0.05 U/kg of body weight/h
     - Post meal "bolus": 0.10 U/kg of body weight for 90 minutes/h

   Basal rate was subsequently adapted according to BG levels by addition or substraction of 0.5 U/h to the previous rate if BG was respectively higher or lower than the fixed values (70-150 mg/dl)

c) Adverse effects
   In case of rapid increase in plasma glucose each element shoul be checked.
   In case of hypoglycaemia IV dextrose 5% had to administered, and insulin infusion rate had to be reduced by half.

3. Maintenance of vein access by continuous saline or glucose solution infusion.

   Permeability of the vein was maintained by infusion of 1- 1.5 lites of neutral solution (saline %0.09) per day.

Patients follow-up: Patients were monitored throughout the study by investigating the occurance of clinical remisssion defined according to the recommendations of International Diabetes Immunotherapy Group (IDIG) as restoration of normal fasting and postprandial blood glucose without any insulin administration for more than two weeks (14) Moreover, integrated measures of metabolic control [insulin dose, glycated haemoglobin (HbA1c), fasting and/ or stimulated serum C-peptide, full blood count, liver function tests, serum total cholesterol, triglycerides, uric acid and serum creatinin, immunologic analysis (ICA, IAA)] analysed after 3,6,12,24 and 36 months.

Data collection and handling: Detailes of clinical data throughout the period of observation was collected and kept in special patients' forms.

Blood collection and storage : Serum and whole blood were stored at -20°C and analysed in laboratories of Instute for Experimental Medical Research, İstanbul University.

Data analysis : Interim analysis was performed every 6 months. Student's t test was used to evaluate the interaction between prognostic factors.

Consent form for the study: Written consent from the patient for participating in the study was obtained.

Results

Clinical measurements such as age, sex, date of onset of symptoms, weight, height, were taken mainly at presentation. General characteristics of patients at onset was listed in Table 1.

All patients had positive ıslet cell antibodies (ICA) in their serums; İnsulin autoantibodies (IAA) levels

Table 1. Characteristics of patients at entry.

N	:	10
Female / Male	:	4/ 6
Mean chronological age (years)	:	14.8 ± 6.3
Fasting Blood Glucose (mg/ dl)	:	336.8 ± 78.1
HbA1c(%)	:	11.7 ± 4.3
C peptid (ng/ ml)		
Basal	:	0.64 ± 0.3
Stimulated	:	1.18 ± 0.64
Insülin dose (IU/ kg/ day)	:	0.89 ± 0.24

were normal range in all patients. No pathology was found in the other labarotory tests.

Patients were treated with intravenous insulin infusion at diagnosis for 2-4 days and then IIT continued with four daily injections for at least 6 months (till remission was spoilt). A complete remission (CR) was observed in 50% of cases (5 patients); additionaly in three patients insulin requirements reduced to an incomplete remission (ICR) level (30%) No remission (NR) was obtained in the remaining two (20%). The rate of remission status can be seen in Figure 1.

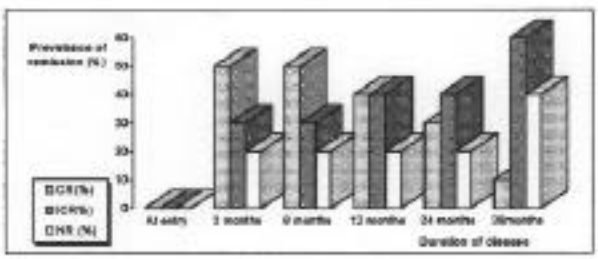

Figure 1. Percent of patients according to remission period during 3 years follow-up.

Based on remission status, initial characteristics [sex, F/M, mean age onset (years), basal and stimulated C-peptide levels (ng/ml)] were listed in Table 2.

All groups were evaluated at 3., 6., 12., 24. and 36. months in terms of remission status and beta cell insulin capacity.

Evaluated insulin requirements, HbA1c levels, beta cell insulin capacity (C-peptide) of all groups at 3., 6., 12., 24. and 36. months, according to remission status, can be seen in Figures 2. 3. 4.

Table 2. Characteristics of patients according to remission status after IIT.

		CR	ICR	NR
N	:	5	3	2
Female / Male	:	1/ 4	3 / 0	2 / 0
Mean chronological age (years)	:	19.1±6.3	15.4±5.3	13.8±2.4
Fasting Bloog Glucose (mg/ dl)	:	111.9±18.2	118.3±20.7	168±18.7
HbA1c (%)	:	7.8±2.1	8.1±3.2	9.3±2.9
Initial C-peptid (ng/ ml)				
Basal	:	1.08±0.39	0.61±0.43	0.28±0.20
Stimulated	:	1.8±0.4	1.01±0.56	0.46±0.19
Initial insulin dose (IU/ kg/day)	:	0.78±0.24	0.89±0.24	1.09±0.42

CR : Complet remission: No insulin requirement after IIT

ICR : Incomplete remission. Lesser than 0.25 U/ kg/ daily insulin requirement

NR : Daily insulin intake > 0.25 U/kg

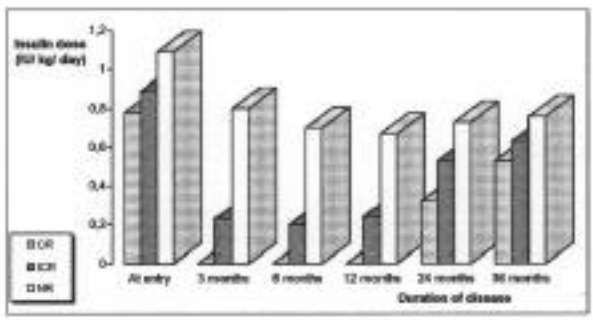

Figure 2. Insulin Dose (IU/kg/day) at home during 3 years follow-up.

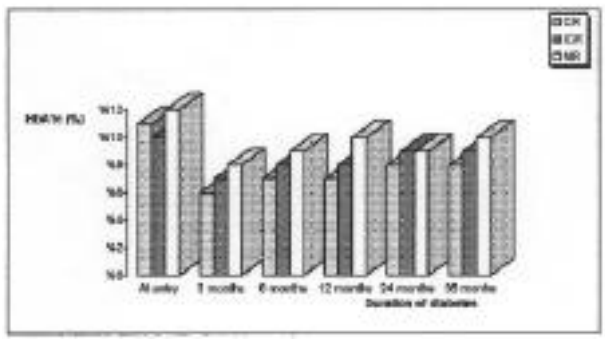

Figure 3. Glycosylated Haemegobin (HbA1c) during follow-up period.

CR patients had higher beta cell reserves than did ICR and NR patients at onset, as defined by percentage increase in serum C-peptide after glucagon stimulation ($p < 0.05$ vs. NR, although CR vs. ICR was not significant) CR group had better metabolic control (HbA1c levels) and significantly higher beta cell reserve than ICR and NR groups at

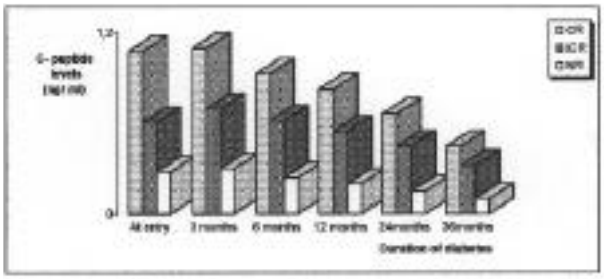

Figure 4. Basal C-peptide levels during 3 years follow-up.

follow-up (P<0.5 vs NR, although CR vs. ICR was not significant).

Mean length of the remission in CR group was 12.4 months. Remission for more than 2 years was in only one case The mean duration of remission for CR was found to be remarkably longer than ICR and NR groups (p<0.01)

It was observed that insulin requirement at onset was not a predictive value in achieving to remission; but daily insulin intake in CR group falled quicker and much more than the other groups (p<0.1).

Conclusions

Clinical remission of IDDM, with reduction of the insulin requirement, was recognized soon after the introduction of insulin, but its association with partial recovery of B- cell function did not become apparent until endogenous insulin secretion could be measured by means of assays for C- peptide. Subsequent studies revealed that improved endogenous secretion of insulin was associated not only with reduced insulin requirements but also with improved glycaemic control and enhanced insulin sensitivity (15,16). Trials of intensified insulin therapy in humans with IDDM have suggested that this intervention can preserve B- cell function. Shah et. al. reported a randomized trial of IIT on recent-onset type 1 diabetic patients (8). The frequency of complete remission as a response to IIT has been reported to be between 33 to 66% in recent-onset IDDM patients by other groups, including ours (6,23).

Although the effect of insulin at this phase is explained mostly through elimination of glucotoxicity and beta-cell rest, there is some evidence to suggest that insulin therapy can also modulate the immun system and the expression of antigens in the islets. It is known that cytokines such as interleukin-1 can either directly or indirectly, by causing the release of inflamatory mediators like prostaglandin E2, supress beta cell function. Although not yet proven, it may be spaculated that insulin may have a modulatory effect at this level as well.

When IIT is administered to recent-onset type 1 diabetic patients, three groups of patients can be discerned, including: Complete remission (CR); incomplete remission(ICR)- insulin requirement falls 0.25 IU/kg/ day-; no remisssion(NR) -impossible to reduce insulin dosage below 0.25 IU/ kg/ day.

The present literatür is, in fact, limited to factors which may predict the occurance of remission. To this end importance of age, sex, initial C-peptide levels in the prediction of remission has been well-established, although there are contradictory reports about the presence of ICA's and probability of remission. An understanding of the mechanisms underlying the occurrence of remission is at present lacking.

Although number of patients was limited in this study, CR was obtained 50% of patients and we can conclude that intensified insulin therapy of newly diagnosed IDDM patients (with intravenous administration at the beginning) may induce remission in the earlier period of the disease and prolonge remission . But it is not clear whether this is a direct effect of insulin or simply due to improved glycaemic control and alleviation of glucose toxicity (17,19). The beta-cell recovery leading to complet remission with IIT depends not only on the magnitude of improved endogenous insulin secretion due to removal of the suppressive effect of glucose toxicity on the intact beta cells and allowing them to rest but also on the relieved body's sensitivity to insulin (16,20). It was obtained that predominantly females at younger ages did not have complete remission. As suggested by our results and by trials of other groups, rapid beta-cell destruction (younger age group and predominantly females) may be associated with lack of metabolic compensation following IIT. At this

point it possibly could be come from different hormonal changes at pubertal ages.

This study and also previous studies by our group have revealed that male gender, disease onset during late child hood and a higher beta cell reserve at clinical onset may point to a possible complete and/ major long-term remission (6,9,19, 21).

Although the mean length of remission in CR was significantly higher than in the NR, all patients, except one, required insulin between 9 months and 18 months of follow-up. In these patients, the decrease in insulin requirement displayed a lineer pattern and the integral of this lineer curve correlated negatively with the basal C-peptide level at clinical onset. The fasting C-peptide levels at diagnosis and the stimulation capacity may be an indicator of probable development of complete remission following IIT. As supported to this knowledge, in this study C-peptide levels in CR was higher than the other groups. At this point it was discussed CR obtained in the study was a possibility of natural remission. Natural remission (spontaneous remission, honeymoon) and IIT-induced complete remission are terms which are currently used interchangeably in the diabetes literatür. Our own initial perception was that IIT-induced complete remission was an accelerated form of natural remission. As the number of patients in both types of remission increased we observed distinct differences between the two groups (19). For example, we observed that spontaneous remission occurs much later in the course of disease (after 3 months) than does IIT-induced remission. This is interesting because it is difficult to induce remission by IIT in long-standing disease. Spontaneous remission in females is also less common than in males. In addition the mean age of patients in spontaneous remission is significantly higher than the mean age of patients experiencing IIT-induced remission. The fasting and stimulated C-peptide levels of patients at the onset of remission are also significantly higher in patients with natural remission. Our results suggests that the remission induced by IIT(early remission) may be a different phenomenon to the natural remission observed later in the course of the disease.

This was one of the first studies that adressed the question of clinical remission with IIT and proposed that starting IIT with insulin infusion at onset was very important to obtain an early clinical remission. Data indicated that this phenomenon was even more frequent than expected without immune- intervention. Information obtained in this pilot study may be usefull in designing multicenter trials.

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